Biliary Atresia: A Case Report

Leah Levey

Abstract

Biliary Atresia (BA) is characterized by a progressive obliteration of all, or part of, the extrahepatic biliary tree[1,5]. It is the primary indication for pediatric liver transplantation, responsible for approximately 50% of all pediatric liver transplants[1-6]. The resting energy expenditure of children living with BA is 30-50% higher than that of healthy children of the same age because children with BA must consume additional calories to promote liver regeneration[6,9,10]. BA prevents bile from traveling from the liver into the intestine, where it is crucial for fat absorption. Bile insufficiency in the intestine results in malnutrition, malabsorption, and fat-soluble vitamin (ADEK) deficiencies. Sixty to 80% of children with end-stage liver disease exhibit moderate to severe malnutrition before liver transplantation[12]. By examining a child living with BA hospitalized at UNC-Hospitals, I explored the medical nutrition therapy for patients with BA before liver transplantation. According to the most recent research, the best nutritional treatment for BA patients before liver transplantation includes cycled EN nocturnal feeding with daily oral feeds using formula with a high MCT:LCT ratio[10,19]. To prevent deficiencies, it is strongly recommended that BA patients be provided with 130-150% of the caloric DRI for age, 2.5-3 g/kg/d of protein, and ADEK supplements[10,11,32].

Introduction

Biliary Atresia (BA) occurs world wide, affecting approximately 1 in 8,000 to 1 in 18,000 of live births[1-4]. BA is characterized by a progressive obliteration of all, or part of, the extrahepatic biliary tree[1,5]. When the extrahepatic biliary tree is damaged, bile is unable to travel from the liver into the intestine, causing bile entrapment in the liver leading to cirrhosis, and resulting in malabsorption of fats in the intestine. BA presents within the first three months of life and is the most common indication for pediatric liver transplantation, responsible for approximately 50% of all pediatric liver transplants[1-6]. If a BA patient goes completely untreated, the liver will become cirrhotic and the child will die within 18-24 months of life[5].

BA is a clinical phenotype, likely resulting from multiple prenatal and perinatal insults to the hepatobiliary tree[4]. There are at least four phenotypes of BA, however the etiology and pathogenesis of each type remains unknown[1,4]. The two major forms of BA are understood as: 1) *The embryonic form*, which is associated with other congenital anomalies and involves abdominal situs, such as polysplenia and intestinal malrotation, and 2) *The perinatal form*, in which the infant is initially considered healthy, but postnatal events that occur within the first three months of life trigger progressive inflammation and fibro-obliteration of the normally developed biliary tree[2-4,7]. The perinatal form is most common, affecting 80% of BA cases[3,4].

BA patients typically present with hyperbilirubinemia, jaundice, hepatomegaly, dark urine, diarrhea, and/or fatty, pale, acholic stools[4,8,9]. When an infant presents with these clinical

symptoms, a hepatobiliary iminodiacetic scan is performed to observe how bile flows from the liver. If the scan shows minimal bile leaving the liver, an exploratory laparotomy is performed in order to confirm BA.

The primary treatment, other than liver transplantation, is the Kasai procedure, which has most success when performed as early as possible, before three months of age[1,2]. During this procedure, the surgeon removes damaged bile ducts and attaches a loop of the small intestine to smaller ducts that are still draining bile. This enables bile to flow directly from the liver into the intestine[35]. A successful Kasai procedure is designed to prevent cirrhosis development and fat malabsorption[1]. However, due to progressive inflammation and fibrosis of intrahepatic bile ducts, 70% of patients with seemingly successful Kasai procedures eventually develop cirrhosis and require liver transplantation within the first two years of life[2-4].

When jaundice resolves within three months after the Kasai procedure, the 10-year transplant-free survival rate is 75-90%[1]. However, if jaundice continues for three months after the procedure, the three-year transplant-free survival rate is approximately 20%[1]. Failed Kasai procedures are common and often lead to death if the infant does not receive a liver transplant[11]. Infants who have undergone a failed Kasai procedure have not survived beyond 24-36 months without receiving a liver transplant[1,6]. Recent studies show that long-term survival without a transplant can be better achieved in BA patients if the Kasai procedure is performed within the first 30-45 days of life[2]. However, there are no convenient methods to screen newborns for BA, so diagnosis within the first two to three months of life is uncommon[2].

The resting energy expenditure of children living with BA is 30-50% higher than that of healthy children of the same age because children with BA must consume additional calories to promote liver regeneration[6,9,10]. BA prevents bile from traveling from the liver into the intestine, where it is crucial for fat absorption. Bile insufficiency in the intestine results in malnutrition, malabsorption, and fat-soluble vitamin (ADEK) deficiencies. Sixty to 80% of children with end-stage liver disease exhibit moderate to severe malnutrition before liver transplantation[12]. Malnutrition continues during the first year of life because BA patients require time to replenish what was lost before the Kasai procedure and/or liver transplantation[5]. BA patients must replenish fat reserves, muscles, structural proteins, and bone mineralization[5].

Forty percent of infants who underwent liver transplantation have growth failure and developmental delay before transplantation because of loss of muscle mass and structural proteins, impaired bone mineralization, and depleted fat reserves[1,5,6]. Because of intestinal bile insufficiency, BA patients also develop biochemical and clinical deficiencies of ADEK vitamins, which may cause complications such as metabolic bone disease, hemorrhaging, and anemia[1,11]. Stunting remains common in infants with BA, despite nutrition-modified formulas adjusted to properly nourish infants who are deficient in bile acids. Exclusive oral intake may not be effective for appropriate growth in infants living with BA, and therefore enteral nutrition (EN) and vitamin supplementation may be required in order for these patients to receive adequate nutrition[5].

By examining a child living with BA hospitalized at UNC-Hospitals, I will explore the medical nutrition therapy for patients with BA before liver transplantation.

Case study

An African-American female had an uncomplicated gestation and delivery in 2015. The child's primary nutrition source during her first two months of life was Gerber Soy 20 kcal/oz. She was fed a soy-based formula because she had discomfort, gas, and excessive stools when ingesting lactose-based formulas. The child consumed 4 oz. every three hours, for a total of eight feeds/day, totaling 147 kcal/kg/day (123% of the DRI). The child was also given a vitamin D3 supplement.

The child's total and direct bilirubin levels were elevated the first and second day after birth. Her hyperbilirubinemia was likely caused by reduced secretions of bilirubin into the bile, which commonly occurs in patients with biliary obstruction[13]. The bilirubin lab results were her first clinical symptoms of BA. However, she was not diagnosed with BA until about two months later.
A primary care physician saw the child about one month after birth for complaints of fussiness, gas, and difficulty passing stools. The child was passing four white, large stools each day. Her total bilirubin, direct bilirubin, and indirect bilirubin levels (6.74, 3.90, 2.80, respectively) were elevated and the primary care physician noted that the child appeared jaundiced. The primary care physician referred the patient to a pediatric gastroenterologist, who saw the child one week later. The pediatric gastroenterologist ordered a hepatobiliary iminodiacetic scan which showed a lack of biliary excretion. A pediatric surgeon performed an exploratory laparotomy when the child was two months old. BA was confirmed during surgery, and the Kasai procedure was performed without complication. However, a CT scan three months after surgery showed that the Kasai procedure had failed.

After the Kasai procedure, the patient experienced multiple complications, such as jaundice, ascending cholangitis, suspected varices, and gastrointestinal (GI) bleeding. At 17 months of age, she was hospitalized because of GI bleeding and was diagnosed with systemic inflammatory response syndrome and severe anemia. During this hospital stay, she experienced hypovolemic shock. GI bleeding has continued and the medical team has been unable to find the source of the bleed.

<u>Nutrition Interventions:</u>
After the Kasai procedure at two months old, the child was not given food orally until her bowel function returned. Her diet was advanced to Pregestimil 20 kcal/oz, a formula provided to patients who have difficulty absorbing fats[14]. However she refused the Pregestimil. It is likely the child is lactose intolerant because she presented with gas and discomfort after consumption of lactose-based formulas, such as Pregestimil. So, she was instead fed Prosobee, a soy-based formula primarily used to decrease fussiness and gas[15]. She also received an ADEK supplement.

She was discharged five days after surgery and consumed Gerber Soy formula and Prosobee formula at home. Gerber Soy and Prosobee are formulas made by different companies, however are both soy-based, lactose-free formulas that contain similar proportions of macro- and micronutrients[15,16]. ADEK supplementation continued.

At six months old, the child began to eat baby foods while also consuming Prosobee. During more recent hospital stays, at age 15-17 months, the child has been eating baby foods while drinking Pediasure Peptide mixed with soymilk. Pediasure Peptide is a peptide-based formula that is easier for children with malabsorption, maldigestion, and other GI conditions to digest[17]. Despite taking ADEK supplements throughout her life, at 17 months old, her vitamin D level was less than 5ng/mL, showing that she was not absorbing ADEK vitamins.

Patient Growth:
Despite risks for malnutrition and growth failure, the child has continued to gain weight appropriately, currently following the 85th percentile for age (Figure 1). Although she experienced some episodes of weight loss because of vomiting and GI bleeding, her overall growth has been appropriate in length and weight for her age.

Figure 1: Weight-for-length Percentiles (Girls, birth to 2 years)

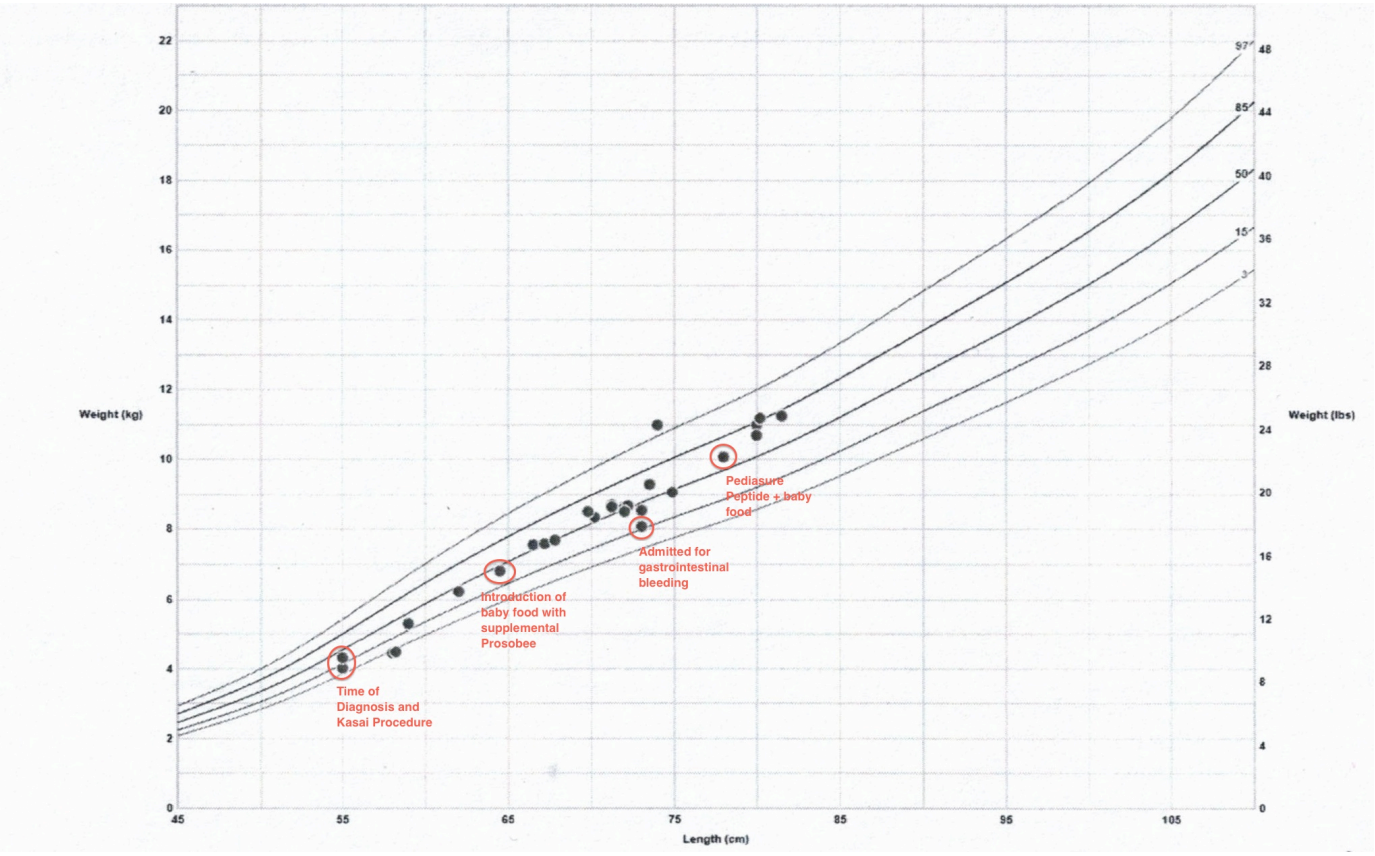

Figure 1 shows the child's growth on a weight-for-length percentile graph of girls from birth to two years of age, highlighting the time of diagnosis, Kasai procedure, medical complications, and nutrition interventions.

Figure 1 shows the child's increased rate of growth after the Kasai procedure. During the time the child was experiencing GI bleeding, the rate of growth decreased, but the patient's overall weight-for-length has steadily and appropriately increased, parallel to the 50th-85th percentiles for age.

Since the child's weight may be misinterpreted due to hepatomegaly and fluid retention, it is crucial to also examine her length independently of her weight in order to fully understand her growth. Figure 2 shows the child's length-for-age when compared to her age group.

Figure 2: Length-for-age Percentiles (Girls, birth to 2 years)

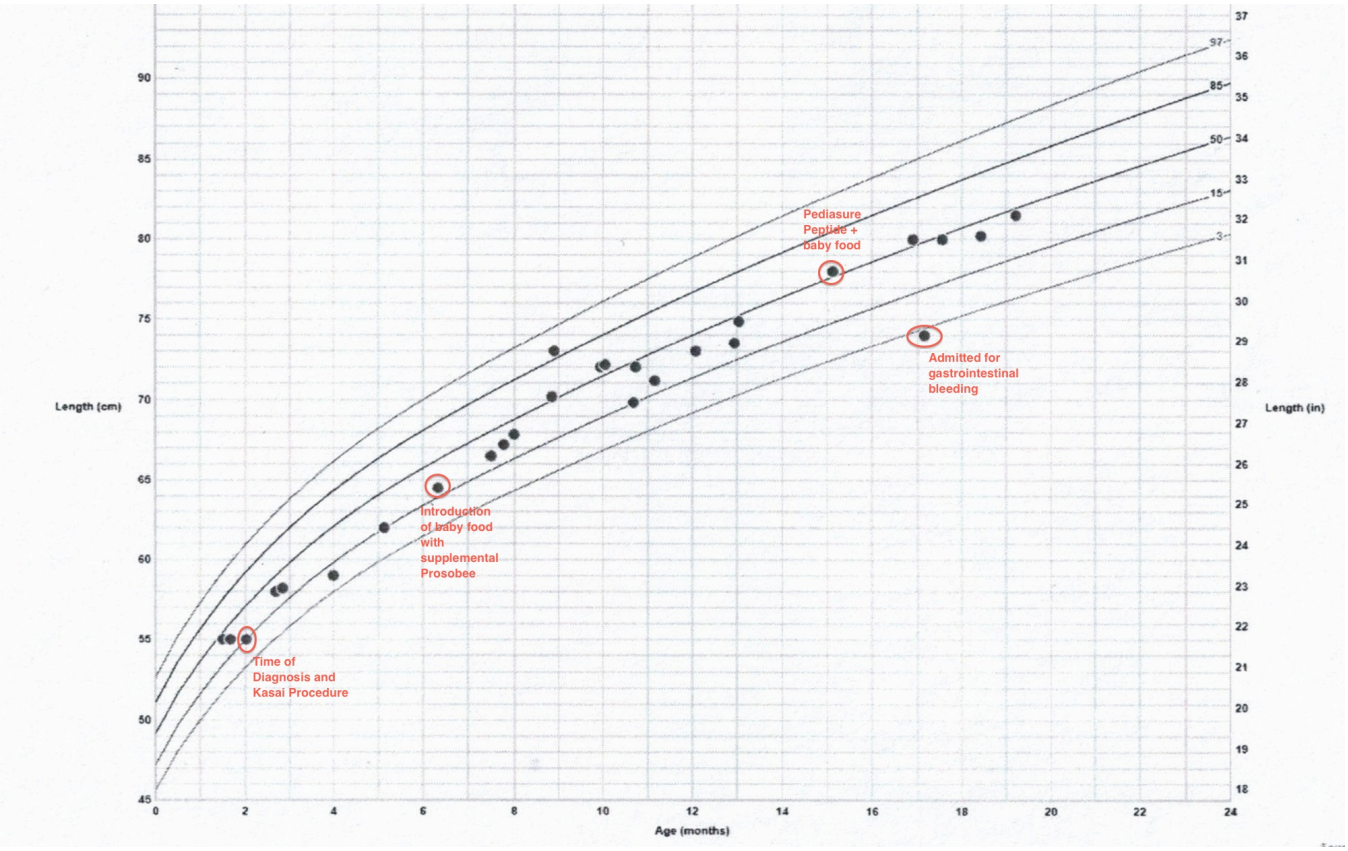

Figure 2 shows the child's growth on a length-for-age percentile graph of girls from birth to two years of age, highlighting the time of diagnosis, Kasai procedure, medical complications, and nutrition interventions.

The child's length increased from the 15th to 50th percentile for age after the Kasai procedure, between 2-8.5 months of age (Figure 2). Her length has remained between the 15th and 50th percentiles while consuming baby foods with Prosobee and baby foods with supplemental Pediasure Peptide. During the time of the child's GI bleeding, length decreased to the 3rd percentile for age. However, overall the child's length-for-age has appropriately increased. Appropriate weight-for length and length-for-age illustrates that the child has shown appropriate overall growth.

Transplant Approval:
The Pediatric End-stage Liver Disease (PELD) is the scoring system used by the Universal Network for Organ Sharing for patients who are eleven years old or younger[18]. It ranks patients on the liver transplant waitlist by measuring bilirubin (a measurement of how well the liver excretes bile), albumin (a measurement of how well the liver maintains nutrition), prothrombin time (a measurement of the liver's ability to make blood clotting factors), growth failure, and whether the child is less than one-year old[18].

The child was approved for the pediatric liver transplant waitlist at 17 months old when her lab values showed an elevated total bilirubin of 4.6, a low albumin of 2.8, and an elevated prothrombin time of 1.16, giving an initial PELD score of 4. To offer a comparison, a PELD score of 15 is the median score of a child at the time of a pediatric liver transplantation[1].

Discussion

Pros and Cons of Liver Transplantation:
Liver transplantation has many risks, including intestinal perforation, hepatic arterial thrombosis, and bile duct strictures[6]. Forty-eight percent of children require additional operations for biliary strictures after receiving a new liver[6]. Although liver transplantation has multiple risks, there are many benefits. For instance, there is an excellent 10-year post liver transplantation survival rate[1]. Furthermore, after a failed Kasai procedure, mortality rates are high for patients who do not undergo a liver transplantation[1,6].

Medical Nutrition Therapy for BA Patients Before Transplant:
Protein-energy malnutrition is a common complication in BA patients before surgery, and may persist after surgery[19]. Effective medical nutrition therapy is crucial for BA patients before liver transplantation because adequate nutrition optimizes results post-operatively[10]. Because of the lack of bile in the intestine, BA patients are at high risk for failure to thrive, malabsorption, and ADEK deficiencies. Growth failure before transplant predicts post-transplant death[6]. Therefore, it is imperative that BA patients receive the proper amounts of macro- and micronutrients. Children with BA require 130-150% of the caloric DRI for age, 2.5-3 g/kg/d of protein, and ADEK supplementation[10]. Increased calories are required to promote liver regeneration[10]. Increased protein consumption is necessary to blunt the catabolic state that is common in a BA patient while improving the patient's growth rate[10]. In children, it is rarely necessary to decrease protein consumption because of hepatic encephalopathy[10]. ADEK supplementation is necessary to prevent any ADEK deficiencies caused by the fat malabsorption that occurs in this population.

Although exclusive breastfeeding during the first six months of life is recommended for healthy infants, those with BA may not benefit because of their increased needs for macro- and micronutrients. Studies show that exclusive breastfeeding of BA patients results in decreased growth because breast milk does not provide enough calories and protein for this population[11]. Patients with BA have elevated estimated needs when compared to the average infant of a similar age because of liver degeneration. Providing supplemental

feeding immediately after the Kasai procedure results in better nutrition outcomes than interventions at a later age or only immediately before transplant[12]. Those with BA require daily supplementation with formula.

Additionally, because breast milk does not supply enough vitamin K for the average infant, it is recommended that all newborns receive vitamin K supplements[20]. Since BA patients are more prone to ADEK malabsorption and deficiency, it is even more crucial that BA patients receive vitamin K supplements to avoid vitamin K-deficiency-related bleeding and death[20].

MCT Formulas:
BA patients have defective fat digestion and absorption because of intestinal bile insufficiency[11]. Bile aids in fat absorption by forming a micelle with the products of triacylglycerol digestion: fatty acids and monoacylglycerol[21]. The formation of micelles allows these products of fatty acid digestion to cross the brush border and enter the mucosal cells of the small intestine. Once in the mucosal cells, fatty acids and monoacylglycerol are reassembled into triglycerides, and then secreted into the lymphatic system as chylomicra[21]. Deficiency of intestinal bile causes defective digestion and absorption of fats because fatty acids and monoacylglycerol are then unable to form with bile and other byproducts to produce a micelle and enter the mucosal cells of the small intestine[11]. However, fats varying in fatty acid chain length are absorbed differently[22]. For instance, the absorption of medium-chain triglycerides (MCTs), which contain six to twelve carbon fatty acids, differs from the absorption of long-chain triglycerides (LCTs), which contain fatty acids longer than twelve carbons[22]. Medium chain fatty acids are absorbed directly into the portal blood and are then transferred directly to the liver for oxidation, whereas the fatty acids of LCTs require bile to enter mucosal cells of the small intestine in order to be absorbed properly and be secreted as chylomicra into the lymph[22].

Dietitians provide formulas with increased MCT:LCT ratios to patients with fat malabsorption because the fatty acids from MCTs are more readily absorbed than those from LCTs[23,24]. MCTs are better absorbed in patients with cholestasis, a group of conditions in which the flow of bile from the liver is defective[4,10].

When infant formula, which provides fat as LCTs, was compared to a formula containing 40% of its fat from MCTs, the MCT-fed infants' stools showed a higher percent absorption of fat compared to the LCT-fed infants (95.2% vs. 89.9%)[23]. In a separate study, premature infants were fed two isocaloric formulas containing either MCTs or LCTs for fifteen days; the alternate formula was given for a second period of fifteen days[25]. While consuming the MCT formula, infants showed greater fat absorption (97.1% vs. 83.4%) and better weight gain (11.5 g/kg/100kcal vs. 7.5 g/kg/100kcal) than when consuming the LCT formula[25]. However, we must not decrease LCTs to less than 10% of the total fat content in the formula in order to prevent essential fatty acid deficiencies[10].

Pregestimil was the first formula offered to the case study patient after her Kasai procedure because it provides a high amount of calories, 24 kcal/oz, while promoting fat absorption with an elevated MCT:LCT ratio of 55:45[14]. Pregestimil is commonly used for

children who malabsorb fat because standard pediatric formulas only have an MCT:LCT ratio of 15:85[26]. The increased MCT:LCT ratio in Pregestimil allows BA patients to better absorb fats. Pregestimil is offered in 24 kcal/oz in order to help meet the increased caloric needs of BA patients[14].

The child refused to drink Pregestimil because of gas and discomfort after feedings, possibly related to lactose-intolerance, so she was given Prosobee instead. Prosobee is a soy-based, lactose-free formula for infants with lactose-intolerance[15]. However Prosobee's MCT:LCT ratio is unknown[27]. As the patient grew older, she was supplemented with Pediasure Peptide in addition to her baby foods. Pediasure Peptide is a nutritionally complete, peptide-based formula, which was created to meet the needs of children with malabsorption[17]. Its primary protein source is hydrolyzed whey[17]. Pediasure Peptide contains a high MCT:LCT ratio of 60:40[26].

Fat-Soluble Vitamins:
Patients with BA lack sufficient amounts of bile in the intestine to properly digest fats and absorb ADEK vitamins. Therefore, ADEK deficiency is common in these patients due to chronic malabsorption[11]. ADEK vitamins are important for many human functions.

Light stimulates 11-cis-retinal, a form of vitamin A, to be converted to all-trans-retinal[28]. This reaction results in rhodopsin becoming opsin, causing a nerve impulse to be sent to the brain, initiating non-color vision[11,28]. Night blindness is a common clinical presentation of vitamin A deficiency.

Vitamin E, as alpha-tocopherol, primarily functions as an antioxidant in the membrane of cells to halt chain reactions of lipid peroxidation[11,29]. Vitamin E deficiency may result in a decline of immune functions, peripheral neuropathy, ophthalmoplegia, and ataxia[11,29].

Vitamin K's most vital role occurs in the blood coagulation cascade. When glutamate is gamma-carboxylated it is able to form calcium bridges between blood platelets and vascular and endothelial cells, allowing the blood to clot[30]. In order to gamma-carboxylate glutamate, vitamin K hydroquinone must be oxidized to vitamin K epoxide[30]. Therefore, vitamin K is essential for blood coagulation. Hemorrhaging, particularly from esophageal varices, is a common clinical symptom of vitamin K deficiency in BA patients[11].

Calcitriol, the active form of vitamin D, is required for the transcellular transport of calcium from the gut lumen into the blood, and is therefore necessary for calcium absorption[11,31]. Calcitriol also stimulates intestinal absorption of phosphorus, mobilization of phosphorus and calcium from the bone, and reabsorption of phosphorus and calcium from the kidney[11,31]. Overall, calcitriol stimulates an increase of serum calcium and phosphorus[31]. Vitamin D deficiency may cause a decrease in serum calcium, leading to calcium deficiency[11]. Therefore, rickets and osteoporosis are common clinical presentations in those with Vitamin D deficiencies[11,31]. Vitamin D levels are low in the majority of BA patients, and remain low even one year after a successful Kasai procedure[32]. The best strategy to increase vitamin D levels in BA patients remains unknown[32]. A recent study

indicates that vitamin D is better absorbed when it is administered with D-alpha-tocopherol polyethylene glycol-1000 succinate (TPGS), a form of vitamin E[10].

Since ADEK deficiencies are common in patients with BA, it is necessary to provide oral ADEK supplements to this population in order to prevent clinical problems[4]. If biochemical and/or clinical signs of ADEK deficiency persist when adequate oral supplementation is provided, parenteral ADEK supplementation is recommended[10].

Oral Intake vs. Enteral Nutrition:
Children with BA have increased nutritional needs and are unable to grow appropriately if exclusively breastfeeding. Although oral intake is encouraged in order to maintain psychological health and develop feeding skills, it is recommended that EN be used to supplement oral intake to achieve adequate nutrition[10,19]. However, controversy lies in how to administer the EN. Some researchers believe that oral intake with continuous infusions of EN will result in less regurgitation, and therefore better growth overall[11]. However, more recent studies found that daily oral intake with cycled nocturnal infusions of EN achieved adequate nutrition for infants with prolonged cholestasis[19]. In this case study, the child was fed formula orally and given ADEK supplements. She received no EN.

Overfeeding BA Patients:
Although it is important to feed BA patients enough to obtain appropriate growth and development, a more successful liver transplant operation, and post-transplant success[6], we must be cautious. A recent study followed a representative cohort of 1,706 individuals who received a liver transplant between the years 1995 and 2007[33]. The study shows that the prevalence of obesity in pediatric liver transplant recipients three years post-transplant is extremely high (19.2%)[33]. The prevalence of obesity in 2-5 year olds who have undergone liver transplantation is significantly higher when compared with the general population[33]. The most prominent predictor of obesity after liver transplantation is obesity before transplant[33]. Therefore, although it is important for BA patients to receive adequate nutrition, we must not overfeed in order to decrease risk for obesity after liver transplantation.

In order to reach the top of the pediatric liver transplant waitlist, the patient must have a high PELD score. If the patient fails to grow normally/adequately, the PELD score is higher. If a BA patient is overfed, the higher weight will result in a lower PELD score and increased time on the pediatric liver transplant waitlist.

<u>Pediatric Liver Transplant Waitlist</u>
The PELD score accounts for laboratory values, such as albumin, bilirubin, prothrombin time, age, and growth failure based on sex, height, and weight at listing[34]. It is common for the BA population to have deceptively low PELD scores because of misinterpreted albumin levels and growth patterns[1,6]. Albumin levels are a better measurement of the extent of liver disease than nutritional status[10]. The assessment of BA patients' body weights may be misleading because of hepatomegaly, edema, and/or ascites[6]. Therefore, it is important to use accurate measurements when evaluating growth. Height is a more reliable measurement than weight when identifying children with chronic malnutrition[10]. However,

triceps skin fold (TSF) and mid-upper arm circumference (MUAC) measurements are the most accurate indicators of body composition because variations in these measurements appear earlier than changes in height[10]. TSF and MUAC measure the amount of subcutaneous fat, and fat is the ideal parameter to measure nutritional status in children with cirrhotic livers because fat is the major form of stored energy in the body[10].

The number of deaths has increased in children waiting for an organ transplant who are less than 12 months old[1]. In response, transplant centers are increasingly appealing Regional Review Boards for exception points[1]. The review boards grant exception points on a case-by-case basis in order for the PELD score to better represent the severity of the patient's disease[1]. There was a five-fold increase in the use of PELD exception points from 2002-2013[1]. Rates of exception score requests are particularly high in children less than twelve months of age living with BA; however those listed with exception scores are more likely to be white and privately insured, suggesting bias[1].

Pancreatic Enzymes*:*
Lipases are enzymes that are excreted from the pancreas into the intestine to aid in fat digestion. These enzymes hydrolyze fats (triglycerides) into monoacylglycerol and fatty acids, which combine with bile and other byproducts to form a micelle. The micelle moves close to the brush border of the mucosal cells of the small intestine to allow lipids to diffuse into the mucosal cells[21]. Since the pancreas is anatomically adjacent to the hepatobiliary system, children with cholestatic diseases were thought to possibly have exocrine pancreatic insufficiency[8]. However, children living with BA were actually found to have elevated serum pancreatic enzyme concentrations when compared to children without jaundice, and therefore did not express exocrine pancreatic insufficiency[8]. These results are compatible with similar research studies[8].

Conclusions

According to the most recent research, the best nutritional treatment for BA patients before liver transplantation includes cycled EN nocturnal feeding with daily oral feeds using formula with a high MCT:LCT ratio[10,19]. To prevent deficiencies, it is strongly recommended that BA patients be provided with 130-150% of the caloric DRI for age, 2.5-3 g/kg/d of protein, and ADEK supplements[10,11,32].

After liver transplantation, it is recommended that total parenteral nutrition be provided for about two days, until the surgical ileus resolves, and then advance the patient's diet to EN. Patients continue to be at high risk for malabsorption after transplant surgery because of previous malnutrition[10]. Therefore, it is recommended that BA patients begin with an elemental formula, which is easier to digest, before advancing to a standard formula[10]. It is also suggested that vitamin D and calcium supplementation continue after liver transplantation to avoid metabolic bone disease[10]. It is crucial to continue monitoring the patient's diet for about three years after liver transplantation in order to confirm that the nutrition being provided is promoting appropriate growth[10].

When examining the growth of a BA patient, it is important to measure fat mass instead of weight. Body weight may be deceptively high in this population due to hepatomegaly and fluid retention. Therefore, TSF and MUAC are the most accurate measures of a BA patient's growth.

The child's PELD score has increased since she was approved for the pediatric liver transplant waitlist because she was given exception points for frequent GI bleeding. Her current PELD score, at 19 months of age, is 35. Her PELD score is now above the median PELD score of a child at the time of pediatric liver transplantation[1].

Resources

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